sion respond to plasmapheresis or prednisone therapy, with or without the additional features of a chronic inflammatory demyelinating polyneuropathy developing. The remaining patients with progression go on to have more confluent distal symptoms and signs typical of distal axonal polyneuropathy and do not respond to immunotherapies.

Progressive lumbosacral polyradiculopathy occurs predominantly in patients with AIDS. Progressive weakness, numbness, and pain of the legs develop subacutely along with impaired sphincter control. A CSF examination is the most important diagnostic test. In polyradiculopathy due to cytomegalovirus (CMV) infection, the CSF typically has a polymorphonuclear pleocytosis (0.5×10^6 per liter or greater), a low glucose level, and an elevated protein content. Ascending paralysis typically leads to death within two months, but early treatment of CMV polyradiculopathy with ganciclovir has been effective in at least some cases. In one patient with a positive CSF VDRL, antibiotic therapy was curative for a syphilitic polyradiculopathy. Other patients have presented with similar neurologic symptoms and signs but with a CSF that had fewer cells and from which CMV could not be cultured. Some of these patients have had lymphomatous cells on CSF cytologic examination, and these patients have died. Others with normal cytologic findings have shown either continued progression or spontaneous remission; the cause in these cases is unknown.

Thus, peripheral neuropathies are common in association with HIV infection, and each type suggests a particular diagnostic and treatment strategy.

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Diagnosing Heavy Metal Intoxication in Patients With Neurologic Signs

NERVOUS SYSTEM SIGNS are common in acute and chronic cases of heavy metal poisoning. These include peripheral neuropathy from lead, arsenic, organic and inorganic mercury, and thallium; mental retardation or dementia from organic and inorganic mercury and lead; psychosis from arsenic and inorganic mercury; encephalopathy with seizures from lead and arsenic; and visual disturbances or ataxia from organic mercury.

Most toxicology laboratories use atomic absorption spectroscopy to analyze specimens for heavy metals. This method can detect common heavy metals, is accurate and quantitative, and can be done on blood, urine, hair, or other tissues. The toxicology laboratory should be informed which heavy metals are suspected because the instrument must be adjusted for each element analyzed. The choice of specimens to submit depends on how recent the exposure was and the duration of the intoxication. In general, blood is the most useful specimen in acute intoxications (within three days), except for arsenic (where, because of arsenic's short half-life, urine is also helpful). For chronic intoxications (weeks to months), urine or hair provides the most useful information.

Care should be taken in collecting specimens to avoid environmental contamination. Whole blood is preferred over serum for heavy metal analysis because metals often accumulate within erythrocytes. The blood specimen should be collected in a heparinized, trace metal-free glass tube. A 24-hour urine specimen should be collected in an acid-washed container (the inside of a plastic or glass container is washed with a solution of 0.1 molar hydrochloric acid, rinsed with distilled water, and then dried). Hair can be used to detect chronic metal intoxications from arsenic and mercury. For the specimen, 50 to 100 strands of scalp hair are cut close to the scalp. The strands are oriented so that the bases of the hairs are together. The bundle of hair should then be cut into thirds and each group of hair strands separately placed into trace metal-free glass tubes that are labeled proximal, middle, or distal scalp hair. A metal measurement of all three specimens will provide an estimation of the duration of the exposure because hair grows about 1 cm per month. Differences in metal content in the three hair sections also decrease the likelihood that the metal accumulation occurred from external environmental contamination, such as from hair washing.

In interpreting heavy metal analyses, it is important to know the normal values from a particular toxicology laboratory. In general, levels that are consistent with significant heavy metal intoxication are at least twofold to threefold above the normal levels for a laboratory. If borderline levels of lead or another heavy metal occur in a patient thought to have chronic intoxication, a diagnostic challenge with calcium disodium ethylenediaminetetraacetate (EDTA) may be considered. In this situation, a baseline 24-hour urine specimen is collected. A second 24-hour urine collection is started and the adult patient is given EDTA, 1 gram in 250 ml of 5% glucose solution given intravenously over one hour. The EDTA dose is repeated 12 hours later. A pronounced increase in the heavy metal content in the second urine collection, usually threefold to fivefold over the baseline specimen, implies substantial exposure to the heavy metal with increased body burden.

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New Strategies in Stroke Treatment

THE INCIDENCE OF STROKE has decreased significantly in recent decades, due largely to a better management of risk factors such as hypertension. This improvement has not been matched by the results of treating acute stroke, which has been directed at restoring or amplifying altered perfusion and preventing the aggregation of formed elements of blood. Using aspirin reduces the incidence of stroke after a transient ischemic attack, ticlopidine hydrochloride use is under study, and other antiplatelet drugs have not been shown to be effective. Heparin and sodium warfarin administration reduces the incidence of cardiogenic emboli but is not beneficial in

other types of stroke. The use of anticoagulants in progressing stroke, while customary, has unproven benefits. Thrombolytic agents carry a significant risk of hemorrhage. Dextran sulfate, hemodilution, and pentoxifylline are ineffective.

Our understanding of the pathophysiology of acute cerebral ischemia has attained new levels in recent years. Attention was focused initially on energy substrate availability for ischemic neurons, but high intracellular glucose may increase intracellular acidosis. Other potentially cytotoxic events include alterations of the homeostasis of intracellular ions (especially calcium), an imbalance between prostacyclin and thromboxane production, a net increase in free radical species, and changes in the blood-brain barrier with the formation of edema and subsequent further impairment of the diffusion of oxygen and glucose into the neuron. Each of these has led to the development of a new therapeutic strategy, the results of which are summarized.

The most exciting development in the treatment of cerebral ischemia is recognizing that excitatory and other neuropeptides are released after ischemia and may potentiate cellular damage by augmenting calcium flux into neurons, resulting in their untimely demise.

The mechanisms of the neurotoxicity of calcium influx in ischemia, recently reviewed, are complex. Although calcium channel blockers also affect the vascular tone, recent work indicates that their effect on the calcium homeostasis of the neuron may play a more central role in ischemic damage than previously appreciated. Studies in animals, using centrally acting calcium channel blocking agents such as nimodipine and lidoflazine, have persuasively shown a consistent and substantial beneficial effect on ischemic brain. Furthermore, a single-blind study of the effect of nimodipine use on the clinical course of patients with acute ischemic stroke showed significant functional improvement in the treated group. An additional double-blind study has also shown the use of nimodipine to significantly reduce morbidity and mortality. Currently, multicenter double-blind trials are being carried out to further study the effects of these calcium channel blocking agents in acute cerebral ischemia.

Yet another means of approaching calcium neurotoxicity involves the neurotransmitter mediation of neuronal calcium channels. Glutamate is a known excitatory transmitter found in large concentrations in human cortex and hippocampus. Studies completed in the past 15 years have shown that glutamate is a powerful neurotoxin and that its blockage or antagonism greatly diminishes the sensitivity of central neurons to ischemia. The *N*-methyl-D-aspartate (NMDA) subclass of glutamate receptors has the unique characteristic of being linked to calcium-permeable channels. Studies in animals using both a nonspecific excitatory amino acid-receptor antagonist and specific NMDA-receptor antagonists have shown a decrease in stroke size, deficits, and the percentage of severely ischemic neurons. As yet, there is nothing approved for clinical use.

While experimental data have convincingly shown that administering glucose before cerebral ischemia in animals seriously worsens the postischemic outcome, the interpretation of clinical studies in humans is open to debate. One problem is that the critical variable—intracellular glucose—cannot be measured. Nevertheless, it would seem prudent to minimize administering glucose until more definitive data are available.

Several studies indicate that the main cause of early death in patients with stroke is swelling of the ischemic hemisphere and the resulting transtentorial herniation. The results of clinical trials that have investigated the effect of glycerol or dextran use in acute stroke have been inconsistent. Some studies have shown benefits, some have not.

Additional approaches to metabolic treatment involve prostaglandin biosynthesis. There are several metabolic intermediaries in the synthetic pathway that are potentially harmful to intact neurons. These include active oxygen species (free radicals), thromboxane, and leukotrienes. During incomplete ischemia it is postulated that the normal biosynthetic pathway is altered such that the resultant load of these compounds, normally buffered by the cell, becomes toxic. Studies are being done to assay the effectiveness of drugs thought to scavenge the free radicals and to inhibit the production of thromboxane and leukotrienes. Controversy and conflicting claims surround the results of these studies.

These new strategies, especially those dealing with calcium homeostasis, hold great promise for the management of acute stroke, suggesting that previous therapeutic strategies aimed at treating the circulation may be missing the target: the tissue.

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Vitamin E Use in Neurology

VITAMIN E DEFICIENCY was for many years thought not to occur in humans. Several deficiency states have recently been recognized, however, and some diseases once thought to be untreatable have now been found to be treatable by supplementing vitamin E.

Vitamin E is a fat-soluble substance abundantly present in a normal diet. It is most plentiful in vegetable oils and whole grains, but it is also present in green plants and meat and dairy products. The minimum daily requirement is 8 to 10 mg per day, although patients on total parenteral nutrition require about 50 mg per day. Dosages of as much as 100 to 200 mg per kg body weight per day orally or 1 to 2 mg per kg per day intramuscularly are used to treat deficiency states due to malabsorption. Normal serum levels are between 0.5 and 2.0 mg per dl (0.011 mmol per liter). It is probably more meaningful, however, to measure vitamin E levels relative to the level of total lipids (normal greater than 0.6 mg per gram of lipid), as patients with vitamin E deficiency with normal absolute levels but low relative levels have been reported. Vitamin E works together with selenium to prevent superoxides from peroxidating polyunsaturated lipids in cell membranes.

The clinical syndrome associated with vitamin E deficiency usually resembles a spinocerebellar degeneration with ataxia, hyporeflexia, a loss of proprioception, and sometimes cerebellar tremor. Other manifestations are pigmentary retinal degeneration with or without visual loss, dysarthria and dysphagia, ophthalmoplegia, and dystonic